

## Case Report: REL-1017 Reduces Abnormal Clinician Administered Dissociative States Scale Scores in Patients with Major Depressive Disorder

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### Abstract

**Background.** Dissociative symptoms may be found in a subset of patients with major depressive disorders (MDD). The Clinician-Administered Dissociative States Scale (CADSS) is a 23-item scale for the measurement of present-state dissociative symptoms with good inter-rater reliability and construct validity that can discriminate patients with dissociative disorders. The total CADSS score is derived by adding the score for each of the 23 items. A score of 4 or more on the CADSS is considered abnormal and clinically meaningful. Uncompetitive *N*-methyl-D-aspartic acid receptor (NMDAR) channel blockers have been proposed as a treatment for post-traumatic stress disorder (PTSD). REL-1017 is a novel, low potency, NMDAR channel blocker currently in Phase 3 studies for MDD.

**Methods.** This retrospective case series describes a subset of patients from a double-blind, randomized, placebo-controlled, in-patient 7-day, phase 2 trial of oral, once daily, 25 mg (75 mg loading dose on day 1, first dose) and 50 mg REL-1017 (100 mg loading dose on day 1, first dose) as an adjunctive treatment for MDD. This subset of patients was selected based on abnormal CADSS score at baseline, pre-treatment with the study drug. As part of REL-1017 safety evaluation, the CADSS was administered at four timepoints to all study patients: (a) 30 to 60 minutes pre-treatment at baseline on day 1; (b) 2 hours post-treatment on day 1 (after the first dose of study drug); (c) 2 hours post-treatment on day 7 (after the last dose); and (d) prior to discharge on day 9 (2 days after the last dose).

**Results.** Among the 62 randomized patients, four patients had a CADSS score of at least 4 on day 1 before study drug administration (2 patients in the 25 mg arm [CADSS score 22 and 4]; 1 patient in the 50 mg arm [CADSS score 35]; 1 patient in the placebo arm [CADSS score 6]). Among these 4 patients, starting on day 1, 2 hours post-treatment, the 2 subjects in the 25 mg subgroup (75 mg loading dose) and 1 subject in the 50 mg subgroup (100 mg loading dose) showed a clinically meaningful decrease in their CADSS score, while the single patient in the placebo group showed no change. CADSS scores on Day 1 pre-treatment, day 1 post-treatment, day 7 post last treatment, and on

day 9 prior to discharge were 22-2-6-0; 4-0-0-0; 35-14-9-0, and 6-6-n/a-n/a, for the two patients in the 25 mg REL-1017 subgroup, the single patient in the 50 mg REL-1017 subgroup, and the single patient in the placebo group, respectively.

**Conclusions.** These retrospective case report data potentially signal that REL-1017 may determine rapid and sustained improvement in patients with MDD and concurrent clinically meaningful dissociative symptoms assessed by a CADSS score of 4 or above. Ongoing phase 3 trials with REL-1017 are expected to enroll a total of 1200 outpatients with MDD. These studies will potentially generate additional data that may support the initiation of controlled studies with REL-1017 for the treatment of PTSD.

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## Predicting Potential Drug-Drug-Gene Interactions in a Population of Individuals Utilizing a Community-Based Pharmacy

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### Abstract

**Introduction.** Adverse drug reactions (ADRs) are associated with increased morbidity, mortality, and resource utilization. Drug interactions (DDIs) are among the most common causes of ADRs, and estimates have cited that up to 22% of patients take interacting medications. DDIs are often due to the propensity for agents to induce or inhibit enzymes responsible for the metabolism of concomitantly administered drugs. However, this phenomenon is further complicated by genetic variants of such enzymes. The aim of this study is to quantify and describe potential drug-drug, drug-gene, and drug-drug-gene interactions in a community-based patient population.

**Methods.** A regional pharmacy with retail outlets in Arkansas provided deidentified prescription data from March 2020 for 4761 individuals. Drug-drug and drug-drug-gene interactions were assessed utilizing the logic incorporated into GenMedPro, a commercially available digital gene-drug interaction software program that incorporates variants of 9 pharmacokinetic (PK) and 2 pharmacodynamic (PD) genes to evaluate DDIs and drug-gene interactions. The data were first assessed for composite drug-drug interaction risk, and each individual was stratified to a risk category using the logic incorporated in GenMedPro. To calculate the frequency of potential drug-gene interactions, genotypes were imputed and allocated to the cohort according to each gene's frequency in the general population. Potential genotypes were randomly allocated to the population 100 times in a Monte

Carlo simulation. Potential drug-drug, gene-drug, or gene-drug-drug interaction risk was characterized as minor, moderate, or major.

**Results.** Based on prescription data only, the probability of a DDI of any impact (mild, moderate, or major) was 26% [95% CI: 0.248-0.272] in the population. This probability increased to 49.6% [95% CI: 0.484-0.507] when simulated genetic polymorphisms were additionally assessed. When assessing only major impact interactions, there was a 7.8% [95% CI: 0.070-0.085] probability of drug-drug interactions and 10.1% [95% CI: 0.095-0.108] probability with the addition of genetic contributions. The probability of drug-drug-gene interactions of any impact was correlated with the number of prescribed medications, with an approximate probability of 77%, 85%, and 94% in patients prescribed 5, 6, or 7+ medications, respectively. When stratified by specific drug class, antidepressants (19.5%), antiemetics (21.4%), analgesics (16%), antipsychotics (15.6%), and antiparasitics (49.7%) had the highest probability of major drug-drug-gene interaction.

**Conclusions.** In a community-based population of outpatients, the probability of drug-drug interaction risk increases when genetic polymorphisms are attributed to the population. These data suggest that pharmacogenetic testing may be useful in predicting drug interactions, drug-gene interactions, and severity of interactions when proactively evaluating patient medication profiles.

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## Comparative Effectiveness of an FDA-Authorized Digital Therapeutic to Medications and Cognitive Behavioral Therapy Treating Chronic Insomnia in Adults

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### Abstract

**Introduction.** Chronic insomnia affects the physical and mental health, quality of life, and productivity of 6 to 10% of the adult population (15-25 million U.S. adults). Available treatments include guideline-recommended first-line cognitive behavioral therapy for insomnia (CBT-I) and medications. However, limitations such as patient access to CBT-I and limited efficacy, the presence of significant side effects, as well as safety concerns about medications limit favorable outcomes. Somryst is an FDA-authorized prescription digital therapeutic for the treatment of chronic insomnia in adults. The purpose of this analysis is to compare the effectiveness of the digital therapeutic vs CBT-I and medications for primary insomnia.

**Methods.** Chronic insomnia trials focused on digital therapeutic, CBT-I, or medication were identified in a systematic literature review. Studies using a comparator arm that cannot be considered clinically equivalent to other treatments in the network were excluded (eg, meaningfully different definition of placebo arm). A Bayesian network meta-analysis was performed in R on the mean change from baseline and the proportion of remitters using the insomnia severity index (ISI) endpoint with follow-up time-points between 6 and 12 weeks. Mean change in ISI score from baseline was analyzed as a continuous endpoint while comparisons of the proportion of remitters were performed using odds ratios. The analysis used a random-effects model for the base case analysis. A surface under the cumulative ranking curve (SUCRA) analysis was performed to rank the treatments on each endpoint.

**Results.** In total, 13 studies reported ISI mean change from baseline data. Only the digital therapeutic and CBT-I were significantly different than placebo. The digital therapeutic had the greatest mean change from baseline in ISI from placebo (−5.77 points, 95% Credible Interval (CrI) [−8.53, −3.07]), followed by CBT-I (−4.3 points, 95% CrI [−6.32, −2.39]). In the SUCRA analysis, the digital therapeutic had the highest probability (56%) of being the most effective treatment based on ISI mean change from baseline. Only 8 studies reported the proportion of ISI remitters. Only the digital therapeutic showed a statistically significant difference in remission vs placebo and had the highest odds ratio for remission vs placebo (12.33 95% CrI [2.28, 155.91]). The odds ratio for remission vs placebo in CBT-I was not statistically significant (4.08 95% CrI [0.45, 45.58]). The digital therapeutic had the highest probability (64%) of being the most efficacious for inducing remission per ISI.

**Conclusions.** Somryst was projected to be the most effective therapy on both mean change in ISI and ISI remission within 6 to 12 weeks of treatment start vs either CBT-I or medications. Further investigation should be performed to demonstrate the long-term effectiveness of all chronic insomnia treatments.

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## Outcomes from Engagement and Use of a Prescription Digital Therapeutic to Treat Opioid Use Disorder: A Real-World Pilot Study

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### Abstract

**Introduction.** The opioid epidemic in the United States is getting worse: in 2020 opioid overdose deaths hit an all-time high of 92,183. This underscored the need for more effective and readily available treatments for patients with opioid use disorder (OUD).